Piggyback packaging in the mammary gland.

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The development of the placenta and mammary gland are crucial in understanding the successful evolution of the mammals as a group. The placenta is remarkable for its variations in structure (Wooding & Burton, 2008), conversely the mammary gland secretory mechanism is surprisingly uniform (Wooding, 1977).
The mammary gland probably evolved from a protein producing anti bacterial skin secretion designed to keep the egg moist (Oftedal, 2012).With the advent of the placenta and internal development the requirement changed to nutrient provision for the neonate.
Lipid is more energy rich than protein and the success of the mammary gland depended on the evolution of a unique mechanism for continuous secretion of large amounts of both protein and lipids without damaging the mammary cell.

Protein secretion is by standard exocytosis but each cytoplasmic lipid droplet (CLD) is packaged neatly in a unit membrane separated from the core lipid by a very uniform 15 to 20 nm wide cytoplasmic layer which together form the milk fat globule membrane (MFGM, see figure 1). All mammary glands so far investigated secrete exactly similar milk fat globules (MFGs) but what molecular system the cell uses to achieve this packaging is controversial.
The paper by Monks et al is a valuable contribution to resolving some of the uncertainties in this debate.
Proteomics and biochemical studies of CLD and MFGM have demonstrated that three proteins play important roles in the lipid packaging process: transmembrane butyrophilin (BTN) in the

plasmalemma, adipophilin (PLIN 2) on the surface of the CLD and the cytoplasmic protein xanthine oxidase (XO). Possible scenarios for the exact roles of each are discussed by Jeong et al, 2013.

Monks et al produced a mouse strain with a conditional Cre – Lox deletion of 97% of the XO in the mammary gland only (MGKO mouse). Surprisingly this deletion does not significantly alter the amount of milk produced to adequately nourish the pups.

However the MFG secreted into the milk are considerably larger than in the wild type (WT) and the proteomic array of the MFGM is modified. Monks et al elegant and careful immunofluorescent studies show that in the MGKO mice without XO, the CLD do not associate with the BTN in the apical plasmalemma as they do in the WT. This is the initiation of the normal WT packaging process. Instead their results suggest that the MGKO mice rely on a slower process relying on golgi vesicle exocytosis gradually undercutting an apical CLD. This conclusion is supported by their proteomic results which show that the MGKO MFGM contains significantly more golgi vesicle marker proteins than the WT.

These results are corroborated by EM (Wooding, 1977) and LM immunocytochemical (Wooding and Sargeant, 2015) studies showing a characteristic golgi vesicle close association with the apical CLD in the mammary glands of all mammals investigated adequately so far.

This would be an example of an evolutionary recruitment of the XO to speed up the secretory process and reduce the loss of other cytoplasmic constituents illustrated by the electron micrographs of the MGKO mouse mammary gland in the Monks et al paper.

The golgi vesicles are designed by evolution to exocytose their content, in the mammary gland their preexisting association with the CLD allow the CLD to piggyback their way out of the cytoplasm packaged in plasmalemma and golgi vesicle membrane.

The molecular details of the membrane interactions involved in the uniform packaging of the MFG are still unclear but the Monks et al paper may serve to reignite interest in this important aspect of neonatal nutrition.

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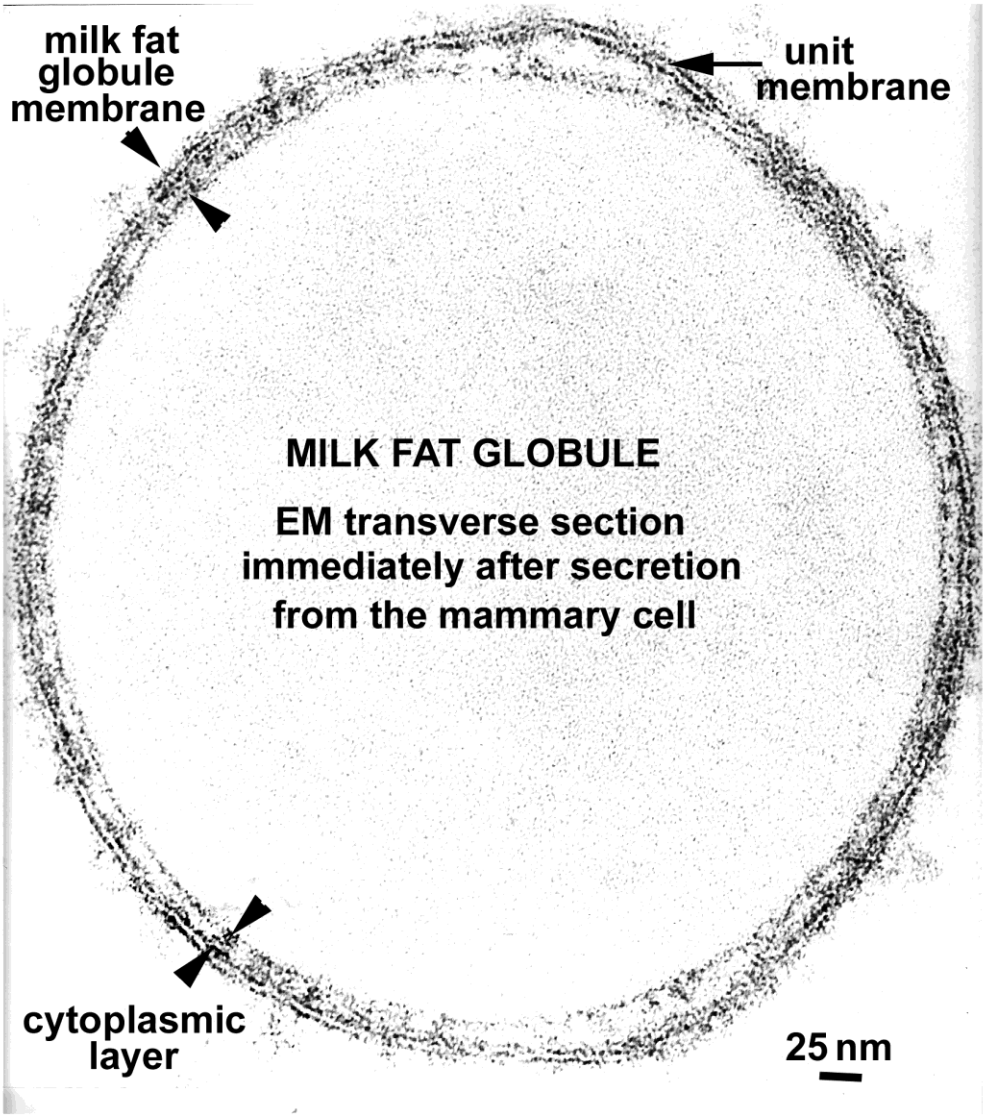

Figure 1. Electron micrograph of typical (small) MFG. This could be from any mammalian species- but in fact is a cow MFG.